REMARKS

Reconsideration of the present application is respectfully requested in view of the above Amendments and the following remarks. Claims 19 and 21-35 were pending. Applicants hereby cancel claims 24, 25, 29, and 31-34 without acquiescence to any rejection and without prejudice to prosecution of the cancelled subject matter in a related divisional, continuation, or continuation-in-part application. Without acquiescing to any rejection, claims 19 and 27 have been amended to point out with greater particularity and to claim distinctly certain embodiments of Applicants' invention. No new matter has been added by this amendment. Support for the amendment can be found throughout the specification as filed, for example, at page 7, lines 8-15; page 37, lines 11-13; page 43, line 21 through page 44, line 14; Table 8; and Figures 3 and 4. Upon entry of the Amendments submitted herewith, claims 19, 21-23, 26-28, 30, and 35 will be pending and under examination.

REJECTIONS UNDER 35 U.S.C. § 103

A. The Examiner rejected claims 19 and 21-35 under 35 U.S.C. § 103(a), asserting that the claimed subjection matter is obvious over U.S. Patent No. 5,726,292 ('292) or Lowell et al. (*Science* 240:800-802 (1988)), in view of VanCott et al. (*J. Immunol. Methods* 183:103-17 (1995)), and in further view of International Patent Application Publication No. WO 95/11700.

Applicants traverse this rejection and submit that the presently claimed subject matter is nonobvious as required under 35 U.S.C. § 103. As an initial matter, Applicants submit that in view of the amendments submitted herewith, which include cancellation of claims 24, 25, 29, and 31-34 without acquiescence or prejudice, the rejection of these claims is moot.

To establish a *prima facie* case of obviousness, the Examiner must show that the cited references teach or suggest all the features of the claim. Assuming *arguendo,* that even if the combination of references teaches each claim feature, the Examiner must provide some articulated reasoning with some rational underpinning regarding why a person having ordinary skill in the art would combine the cited references to obtain the subject matter claimed by the Applicant. *See KSR v. Teleflex, Inc.,* 550 U.S. ___ 1, 14 (2007) ("[A] patent composed of

several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art."). The Examiner must also show that in view of the cited art, a person having ordinary skill in the art would have had a reasonable expectation of successfully arriving at the claimed subject matter. M.P.E.P. § 2143.02 (*citing In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)).

The cited documents, either each alone or in any combination, fail to teach or suggest the presently claimed composition that comprises an antigen consisting of a truncated gp160 as recited, complexed with proteosomes, and combined with bioadhesive nanoemulsions, which composition is formulated for intranasal or respiratory administration and that elicits neutralizing antibodies in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces, and that elicits IgA and IgG antibodies that specifically bind to the truncated gp160 protein and that are present in vaginal secretions, intestinal secretions, lung secretions, and feces. Lowell et al. describe using proteosomes as an adjuvant for enhancing an immune response to peptides; however, the document is silent with respect to using any HIV antigen and is silent regarding any composition comprising proteosomes combined with any antigen *and* bioadhesive nanoemulsions. Neither '292 nor WO 95/11700 describes formulation of gp160 for intranasal or respiratory administration but instead describes a composition comprising an HIV gp160 antigen that is delivered subcutaneously ('292) or parenterally (WO 95/11700) and that induces a serum IgG response. VanCott et al. do not teach or suggest that the gp160 antigen described therein is capable of eliciting neutralizing antibodies or that the antigen is capable of eliciting any antibodies in any mucosal secretion (*e.g.,* vaginal, intestinal, lung secretions, or feces). Thus, the cited references taken together fail to teach or suggest each feature of the claimed composition and fail to suggest or prompt a solution for identifying a composition comprising a truncated gp160 protein that elicits neutralizing antibodies to HIV and that elicits IgG and IgA specific antibodies in mucosal secretions.

Even assuming, *arguendo*, that the cited references, alone or in any combination, teach or suggest each feature of the present claims, at the time of Applicants' invention a person having ordinary skill in the art would have had no reasonable expectation of successfully obtaining Applicants' claimed embodiments by combining the teachings in the cited references.

Furthermore, a reasonable expectation of success must be found in the prior art, and cannot be based on either Applicants' disclosure or later publications. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

While persons skilled in the HIV art have appreciated that certain epitopes (*e.g.,* the epitope(s) in a region designated V3) of gp160 could elicit neutralizing antibodies, persons skilled in the art also have recognized the continued failures and difficulties of developing a useful vaccine that comprises the *env* gene products (the precursor gp160, and the mature gp120 and gp41 polypeptides). Moreover, in the absence of the present application describing an immunogenic composition comprising the truncated gp160 protein, as recited, for inducing a neutralizing antibody response against HIV, a person having ordinary skill in the art would not have reasonably expected that formulating the truncated gp160 as described in the present specification and recited in the instant claims would induce neutralizing antibodies in mucosal secretions and that full-length gp160 *would not*.

As shown in VanCott (*J. Immunol.* 160:2000-12 (1998)), full-length gp160 formulated with proteosomes and emulsomes and administered intranasally to animals *failed* to elicit neutralization antibodies in vaginal washes and was less effective than the o-gp160(451) antigen in eliciting neutralizing antibodies present in lung washes (*see* Table IV, page 2009). VanCott et al. (*supra*) summarized that the data presented therein "are the first data demonstrating locally produced HIV-1 neutralizing Abs [antibodies] in the respiratory or genital tract resulting from immunization" (page 2001, last sentence of introduction). Applicants note that this publication was authored by the three named inventors of the present application and that the data presented therein in Table III and Figure 4 are the data presented in the present application in Table 8 and Figure 4, respectively. A reference must be considered in its entirety (*i.e.,* as a whole), including portions that would lead away from the claimed invention (*see W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). Moreover, the data presented in VanCott (*supra*, 1998) illustrating a composition comprising full-length gp160, proteosomes, and emulsomes lacked the desired immunological properties, particularly the inability to induce sufficient neutralizing antibodies, if available at the time of filing, would lead a person of ordinary skill in the art away

from making the claimed compositions that include a truncated gp160. Thus, contrary to the assertion by the Examiner, the claimed compositions do *not* flow naturally from the teachings in the prior art (*see* the Action, page 6) but instead have been obtained *despite* the teachings in the prior art.

In addition, the presently claimed subject matter encompasses more than a mere substitution of antigens, as asserted by the Examiner (*see* the Action, page 7). Applicants submit that "increased immunogenicity" of an antigen is not synonymous with eliciting a *particular type* of immune response, as recited in the claims (*see* Action, top of page 6). Amended claim 19 (and thus claims 21-23, 26-28, 30, and 35 that depend directly or indirectly therefrom) recites that the composition elicits neutralizing antibodies to HIV in one or more of vaginal, intestinal, and lung secretions, and feces and elicits specific IgA and IgG antibodies in each of vaginal, intestinal, and lung secretions, and feces. The mere potential for "improved immunogenicity," which the Examiner asserts is taught in WO 95/11700, for example, may arguably provide a reasonable expectation of success in eliciting an improved IgG serum response using full-length gp160, but fails to provide the same expectation of success for eliciting neutralizing antibodies and eliciting a specific IgA and IgG response in mucosal secretions using a different HIV antigen having a different tertiary structure, such as a truncated gp160. VanCott et al. (1995) recognize the difficulties in formulating gp160, as described therein, so that conformational integrity of the polypeptide is maintained (*see, e.g.,* page 114, second column), further suggesting the nonobviousness of any given gp160 formulation.

When viewing the claim as a whole, and in light of the HIV vaccine art reporting little success in inducing neutralizing antibodies in mucosal secretions by administering HIV envelope-related antigens, the cited references failed to provide a person of ordinary skill in the art with a reasonable expectation of success in arriving at the presently claimed subject matter. Therefore, based on any of the teachings in Lowell et al., '292, VanCott et al., or WO 95/11700, alone or in any combination, a person skilled in the art would not *reasonably expect* that the gp160 antigen described in VanCott et al. if combined with proteosomes and bioadhesive nanoemulsions would elicit neutralizing antibodies in mucosal secretions.

Accordingly, at the time of filing of the present application and in the absence of the application's disclosure, a person having ordinary skill in the art would have had no reasonable expectation of successfully obtaining the claimed compositions. Applicants respectfully submit that the PTO has failed to establish a *prima facie* case for obviousness within the meaning of 35 U.S.C. § 103(a). Applicants therefore submit that the present claims meet the requirements for nonobviousness under 35 U.S.C. § 103 and respectfully request that this rejection be withdrawn.

B. The Examiner rejected claims 19 and 21-35 under 35 U.S.C. § 103(a), asserting that the claimed subjection matter is obvious over WO 95/11700 in view of '292, and in further view of U.S. Patent No. 5,116,740 ('740). The Examiner acknowledges that WO 95/11700 in view of '292 fail to teach a truncated gp160; however, the Examiner alleges that '740 inherently teaches the truncated gp160 disclosed in the instant application, and that a person having ordinary skill in the art would have found it obvious to substitute the protein described in '740 for the gp160 protein described in WO 95/11700.

Applicants traverse this rejection and submit that the instant claims as amended herewith are nonobvious. As stated above, the Examiner must show that the cited references teach or suggest all the claim features, provide some articulated reasoning with some rational underpinning regarding why a person having ordinary skill in the art would have, at the time of the present invention, combined these cited references to obtain the subject matter claimed by the Applicant, and show that in view of the cited documents, a person having ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed subject matter.

The cited documents, either each alone or in any combination, fail to teach or suggest the presently claimed composition that comprises an antigen consisting of a truncated gp160 protein as recited, complexed with proteosomes, and combined with bioadhesive nanoemulsions, which composition is formulated for intranasal or respiratory administration and that elicits neutralizing antibodies in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces, and that elicits IgA and IgG antibodies that specifically bind to the truncated gp160 protein and that are present in vaginal secretions, intestinal secretions, lung

secretions, and feces. Neither '292 nor WO 95/11700 describes formulation of gp160 for intranasal or respiratory administration but instead each describes a composition comprising an HIV gp160 antigen that is delivered subcutaneously ('292) or parenterally (WO 95/11700) and that induces a serum IgG response. The document '740 fails to teach or suggest an immunogenic composition comprising the gp160 polypeptide described therein formulated for intranasal or respiratory administration and that elicits neutralizing antibodies to HIV in a subject. Instead, '740 teaches that the gp160 polypeptide may be combined with an adjuvant to provide *diagnostic utility* in an ELISA (*see* column 4, lines 13-21). Thus, the cited references taken together fail to teach or suggest each feature of the claimed composition and fail to suggest or prompt a solution for identifying a composition comprising a truncated gp160 protein, as recited, that elicits neutralizing antibodies to HIV and that elicits IgG and IgA specific antibodies in mucosal secretions.

Even assuming, *arguendo*, that the combined references teach or suggest each feature of the present claims, at the time of Applicants' invention a person having ordinary skill in the art would have had no reasonable expectation of successfully obtaining Applicants' claimed embodiments by combining the teachings in the cited references. Furthermore, a reasonable expectation of success must be found in the prior art, and cannot be based on either Applicants' disclosure or later publications. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

While persons skilled in the HIV art have appreciated that certain epitopes (*e.g.,* the epitope(s) in a region designated V3) of gp160 could elicit neutralizing antibodies, persons skilled in the art also have recognized the continued failures and difficulties of developing a useful vaccine that comprises the *env* gene products (the precursor gp160, and the mature gp120 and gp41 polypeptides). Moreover, in the absence of the present application describing an immunogenic composition comprising the truncated gp160 protein, as recited, for inducing a neutralizing antibody response against HIV, a person having ordinary skill in the art would not have reasonably expected that formulating the truncated gp160 as described in the present specification and recited in the instant claims would induce neutralizing antibodies in mucosal secretions and that full-length gp160 *would not*.

As shown in VanCott (*J. Immunol.*, *supra*), full-length gp160 formulated with proteosomes and emulsomes and administered intranasally to animals *failed* to elicit neutralization antibodies in vaginal washes and was less effective than the o-gp160(451) antigen in eliciting neutralizing antibodies present in lung washes (*see* Table IV, page 2009). VanCott et al. (*supra*) summarize that the data presented therein "are the first data demonstrating locally produced HIV-1 neutralizing Abs [antibodies] in the respiratory or genital tract resulting from immunization" (page 2001, last sentence of introduction). Moreover, the data presented in VanCott (*supra*) illustrating a composition comprising full-length gp160, proteosomes, and emulsomes lacks the desired immunological properties, particularly the inability to induce sufficient neutralizing antibodies, if available at the time of filing, would lead a person of ordinary skill in the art away from making the claimed compositions that include a truncated gp160. Thus, contrary to the assertion by the Examiner, the claimed compositions do *not* flow naturally from the teachings in the prior art (*see* the Action, page 6) but instead have been obtained *despite* the teachings in the prior art.

In addition, the presently claimed subject matter encompasses more than a mere substitution of antigens, as asserted by the Examiner (*see* the Action, page 7). As discussed above in part (A), the potential for "increased immunogenicity," which the Examiner asserts is taught in WO 95/11700, for example, may arguably provide a reasonable expectation of success in eliciting an improved IgG serum response using full-length gp160, but fails to provide the same expectation of success for eliciting neutralizing antibodies and eliciting a specific IgA and IgG response in mucosal secretions using a different antigen having a different tertiary structure, such as a truncated gp160 protein. Applicants submit that "increased immunogenicity" of an antigen is not synonymous with eliciting a *particular type* of immune response, as recited in the claims (*see* Action, top of page 6). Amended claim 19 (and thus claims 21-23, 26-28, 30, and 35 that depend directly or indirectly therefrom) recites that the composition elicits neutralizing antibodies to HIV in one or more of vaginal, intestinal, and lung secretions, and feces and elicits specific IgA and IgG antibodies in each of vaginal, intestinal, and lung secretions, and feces. VanCott et al. (*J. Immunol. Methods*, 1995)recognize the difficulties in formulating gp160, as described therein, so that conformational integrity of the polypeptide is maintained (*see, e.g.,*

page 114, second column), further suggesting the nonobviousness of any given gp160 formulation.

When viewing the claim as a whole, and in light of the HIV vaccine art reporting little success in inducing neutralizing antibodies in mucosal secretions by administering HIV envelope-related antigens, the cited references failed to provide a person of ordinary skill in the art with a reasonable expectation of success in arriving at the presently claimed subject matter. Therefore, based on any of the teachings in WO 95/11700, '292, VanCott et al., or '740, alone or in any combination, a person skilled in the art would not *reasonably expect* that the gp160 antigen described in VanCott et al. (1995) if combined with proteosomes and bioadhesive nanoemulsions would elicit neutralizing antibodies in mucosal secretions.

Accordingly, at the time of filing of the present application and in the absence of the application's disclosure, a person having ordinary skill in the art would not have a reasonable expectation of successfully obtaining the claimed compositions. Applicants respectfully submit that the PTO has failed to establish a *prima facie* case for obviousness within the meaning of 35 U.S.C. § 103(a). Applicants therefore submit that the present claims meet the requirements for nonobviousness under 35 U.S.C. § 103 and respectfully request that this rejection be withdrawn.

NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner rejected claims 19 and 21-35 for alleged obviousness-type double patenting over claims 1-2, 5, and 7-8 of U.S. Patent No. 5,726,292 ('292) in view of either Anselem et al. (PCT International Publication No. WO 94/26255) or WO 95/11700, and in further view of VanCott et al. (*J. Immunol. Methods*, 1995) and Desai et al. (*Proc. Natl. Acad. Sci. USA* 83:8380-84 (1986)) "as described in the 103 rejection above."

Applicants respectfully traverse this rejection and submit that the presently claimed subject matter is a nonobvious modification of the constructs claimed in '292, is an inventive contribution to the HIV immunotherapeutics art, and is not rendered obvious by the teachings in the other cited references. Applicants note that the document, Desai et al., is not included in the rejections under 35 U.S.C. § 103 in the Office Action dated May 14, 2007.

Applicants submit that in view of the Amendments submitted herewith, which include amendments to claims 19 and 27 and cancellation of claims 24, 25, 29, and 31-34 without acquiescence or prejudice, the rejection of these claims is moot. Moreover, as presently recited, the antigen of the claimed composition *consists of* the truncated gp160 protein as recited, which excludes an added exogenous hydrophobic material and excludes such a hydrophobic material that is attached via one or more endogenous or exogenous cysteine residues to the gp160 protein.

As articulated above in the discussion of the rejections under 35 U.S.C. § 103, to establish a *prima facie* case of obviousness, the Examiner must show that the cited references teach or suggest all the claim features, provide some articulated reasoning with some rational underpinning regarding why a person having ordinary skill in the art would have, at the time of the present invention, combined these cited references to obtain the subject matter claimed by the Applicant, and show that in view of the cited documents, a person having ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed subject matter.

Each of the cited documents, either alone or in any combination, fails to teach or suggest that the presently claimed composition, which comprises the truncated gp160 protein as recited, when complexed to proteosomes and combined with bioadhesive nanoemulsions and when formulated for intranasal or respiratory administration, elicits neutralizing antibodies to HIV in one or more of vaginal, intestinal, or lung secretions or feces and elicits IgA and IgG antibodies that specifically bind to the truncated gp160 protein and that are present in vaginal secretions, intestinal secretions, lung secretions, and feces. Even assuming, *arguendo*, that the cited references, alone or in any combination, teach or suggest each feature of the present claims, at the time of Applicants' invention, a person having ordinary skill in the art would have had no reasonable expectation of successfully obtaining Applicants' claimed embodiments by combining the teachings in the cited references. Furthermore, a reasonable expectation of success must be found in the prior art, and cannot be based on either Applicants' disclosure or later publications. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

While persons skilled in the HIV art have appreciated that certain epitopes (*e.g.,* the epitope(s) in a region designated V3) of gp160 could elicit neutralizing antibodies, persons

skilled in the art also have recognized the continued failures and difficulties of developing a useful vaccine that comprises the *env* gene products (the precursor gp160, and the mature gp120 and gp41 polypeptides). Therefore, based on any of the teachings in Lowell et al., '292, Anselem et al., or VanCott et al., alone or in any combination, a person skilled in the art would not *reasonably expect* that the gp160 antigen described in VanCott et al. if combined with proteosomes and bioadhesive nanoemulsions would elicit neutralizing antibodies in mucosal secretions.

Moreover, as discussed above, in the absence of the present application describing an immunogenic composition comprising the truncated gp160 protein, as recited, for inducing a neutralizing antibody response against HIV, a person having ordinary skill in the art would not reasonably expect that formulating the truncated gp160 protein as described in the present specification and recited in the instant claims would induce neutralizing antibodies in mucosal secretions and that full-length gp160 *would not*. As shown in VanCott (*J. Immunol.* 160:2000-12 (1998)), full-length gp160 formulated with proteosomes and emulsomes and administered intranasally to animals *failed* to elicit neutralization antibodies in vaginal washes and was less effective than the o-gp160(451) antigen in eliciting neutralizing antibodies present in lung washes (*see* Table IV, page 2009). VanCott et al. (*J. Immunol., supra*) summarize that the data presented therein "are the first data demonstrating locally produced HIV-1 neutralizing Abs [antibodies] in the respiratory or genital tract resulting from immunization" (page 2001, last sentence of introduction). Moreover, the data presented in VanCott (*supra*) illustrating a composition comprising full-length gp160, proteosomes, and emulsomes lacks the desired immunological properties, particularly the inability to induce sufficient neutralizing antibodies, if available at the time of filing, would lead a person of ordinary skill in the art away from making the claimed compositions that include a truncated gp160. Thus, contrary to the assertion by the Examiner, the claimed compositions do *not* flow naturally from the teachings in the prior art (*see* the Action, page 6) but instead have been obtained *despite* the teachings in the prior art.

In addition, the presently claimed subject matter encompasses more than a mere substitution of antigens, as asserted by the Examiner (*see* the Action, page 7). As discussed above, the potential for "increased immunogenicity," which the Examiner asserts is taught in

WO 95/11700, for example, may arguably provide a reasonable expectation of success in eliciting an improved IgG serum response using full-length gp160, but fails to provide the same expectation of success for eliciting neutralizing antibodies and eliciting a specific IgA and IgG response in mucosal secretions using a different antigen having a different tertiary structure, such as a truncated gp160. Amended claim 19 (and thus claims 21-23, 26-28, 30, and 35 that depend directly or indirectly therefrom) recites that the composition elicits neutralizing antibodies to HIV in one or more of vaginal, intestinal, and lung secretions, and feces and elicits specific IgA and IgG antibodies in each of vaginal, intestinal, and lung secretions, and feces. Applicants submit that "increased immunogenicity" of an antigen is not synonymous with eliciting a *particular type* of immune response, as recited in the claims (*see* Action, top of page 6). VanCott et al. (*J. Immunol. Methods*, 1995) recognize the difficulties in formulating gp160, as described therein, so that conformational integrity of the polypeptide is maintained (*see, e.g.,* page 114, second column), further suggesting the nonobviousness of any given gp160 formulation.

When viewing the claim as a whole, and in light of the HIV vaccine art reporting little success in inducing neutralizing antibodies in mucosal secretions by administering HIV envelope-related antigens, the cited references failed to provide a person of ordinary skill in the art with a reasonable expectation of success in arriving at the presently claimed subject matter. Therefore, based on any of the teachings in '292, Anselem et al., WO 95/11700, VanCott et al., or any other art, alone or in any combination, a person skilled in the art would not *reasonably expect* that the gp160 antigen described in VanCott et al. (1995) if combined with proteosomes and bioadhesive nanoemulsions would elicit neutralizing antibodies in mucosal secretions.

Accordingly, at the time of filing of the present application and in the absence of the application's disclosure, a person having ordinary skill in the art would have had no reasonable expectation of successfully obtaining the claimed compositions. Accordingly, Applicants submit that the presently claimed subject matter is nonobvious and therefore does not unjustifiably extend the exclusivity of patent '292. Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully submit that claims 19, 21-23, 26-28, 30, and 35 are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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